1918 Influenza Virus:
An Overview of the Pathogenicity and Virulence Factors (Part 1: Epidemiology)

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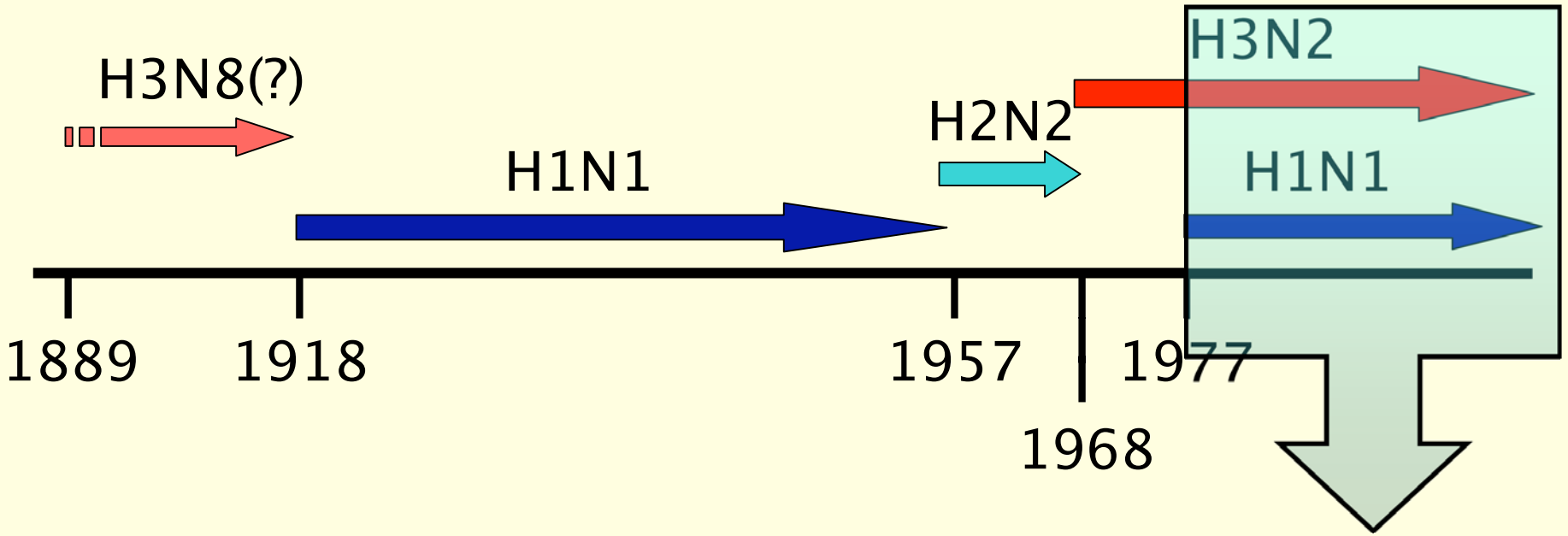
Human Influenza A Timeline



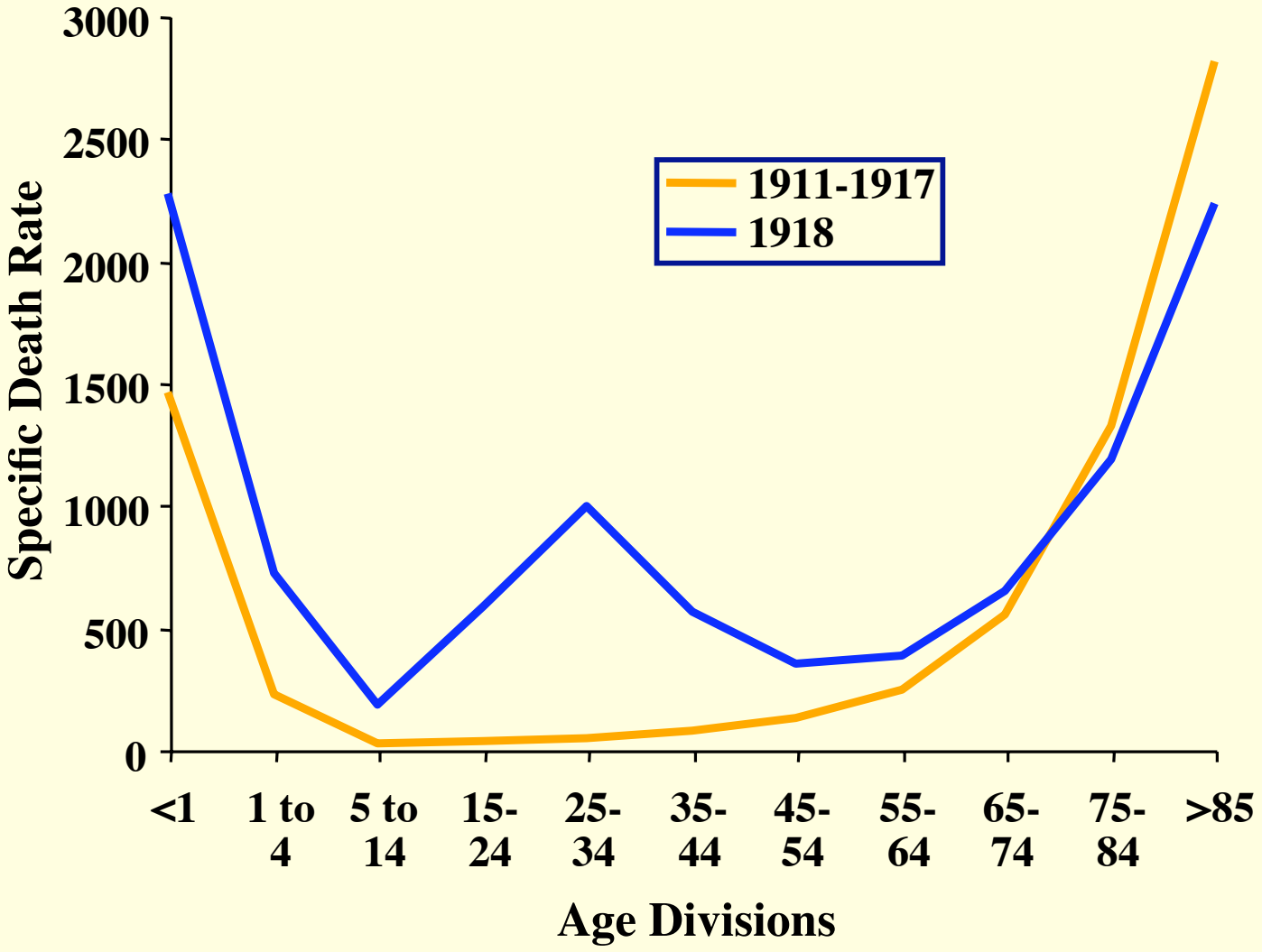
- Both H1N1 and H3N2 co-circulate, and strains of each subtype are included in the annual trivalent vaccine (along with an influenza B strain)
- *No circulation of H2 subtype viruses since 1968*; those <40 years old lack H2 immunity

1918 mortality impact

- 97.5% of clinically infected had a self-limited course of influenza
  - in the absence of vaccines, antivirals, antibiotics, or respiratory support
- Case fatality rate: ~2.5%
- 97% deaths due to secondary bacterial pneumonias
- Serology demonstrated that ~100% individuals were exposed in 1918-1919
  - ~1/3 population clinically ill
  - Total case fatality rate ~0.8%

Taubenberger *et al* 2001 Phil Trans R Soc London B 356:1829-39

Unique pattern of influenza and pneumonia deaths by age in 1918



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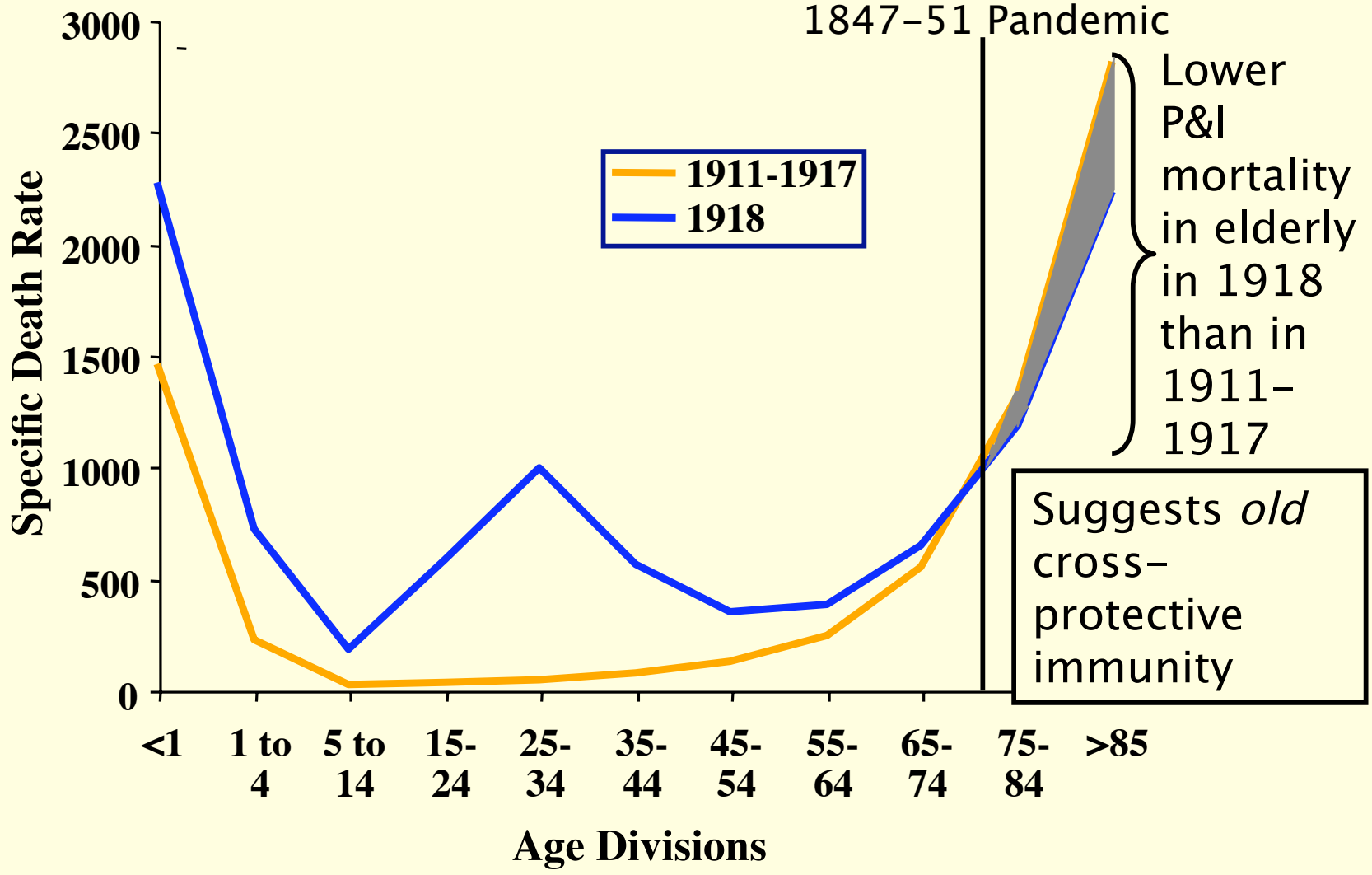

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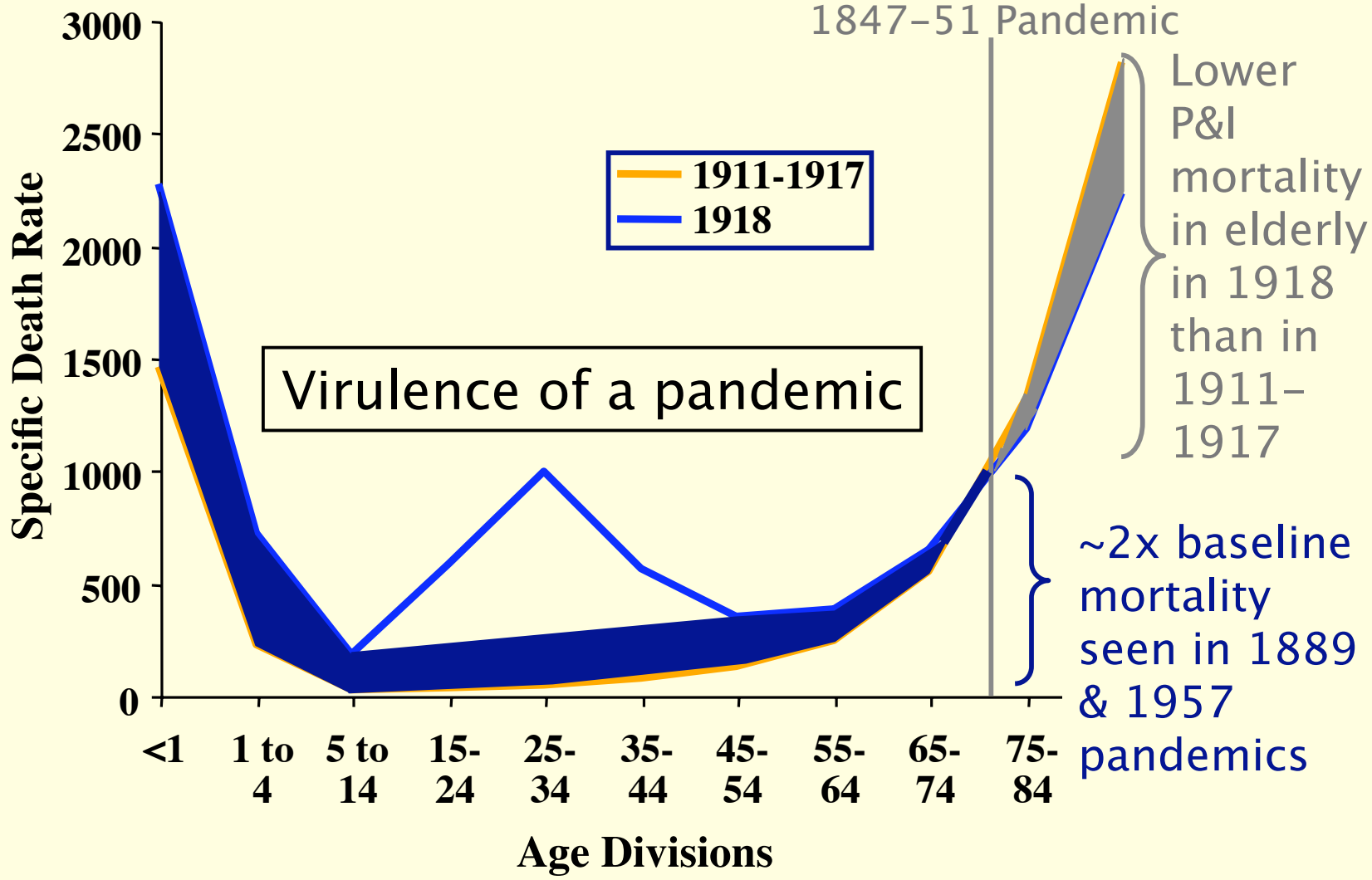

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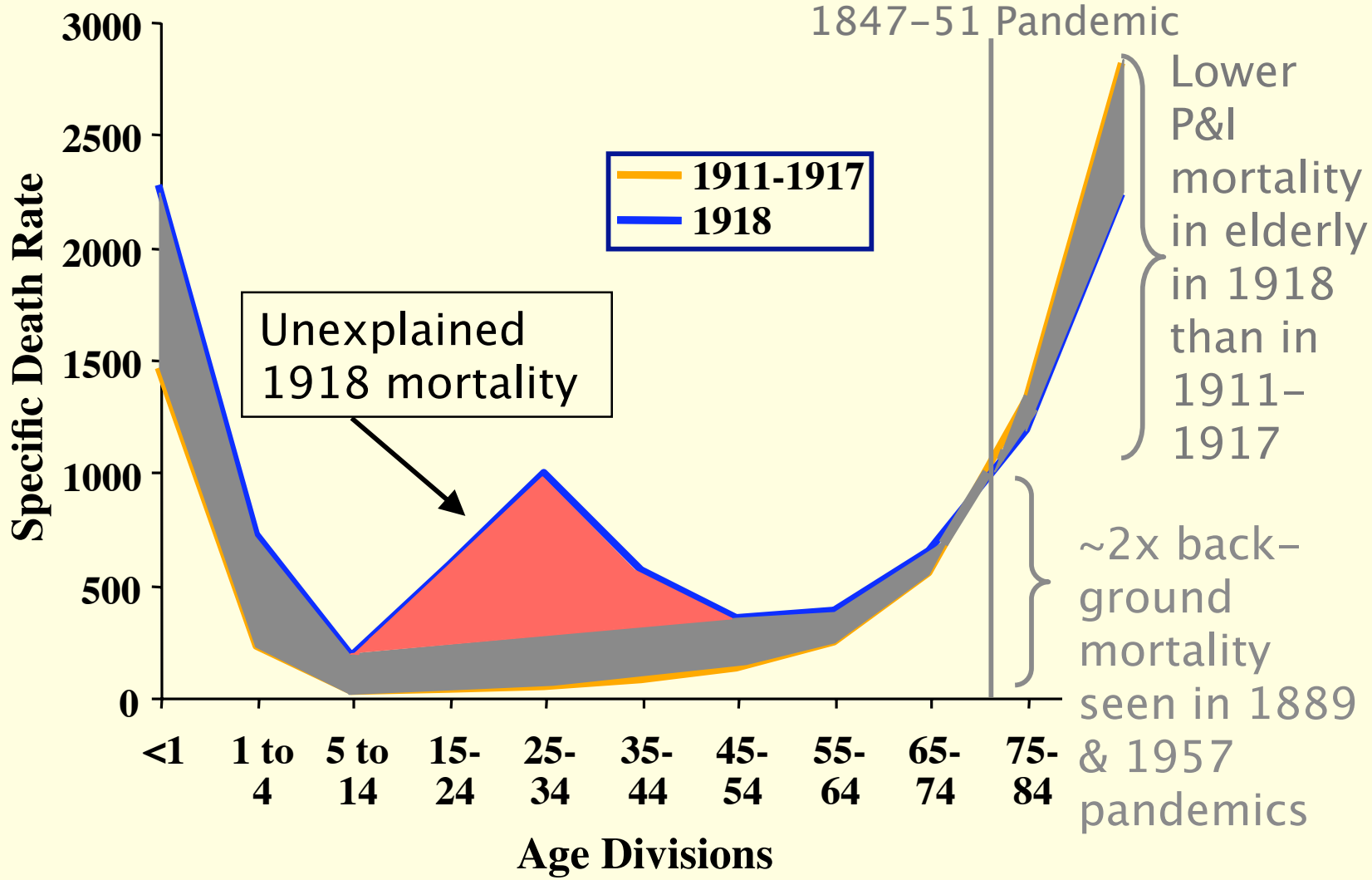

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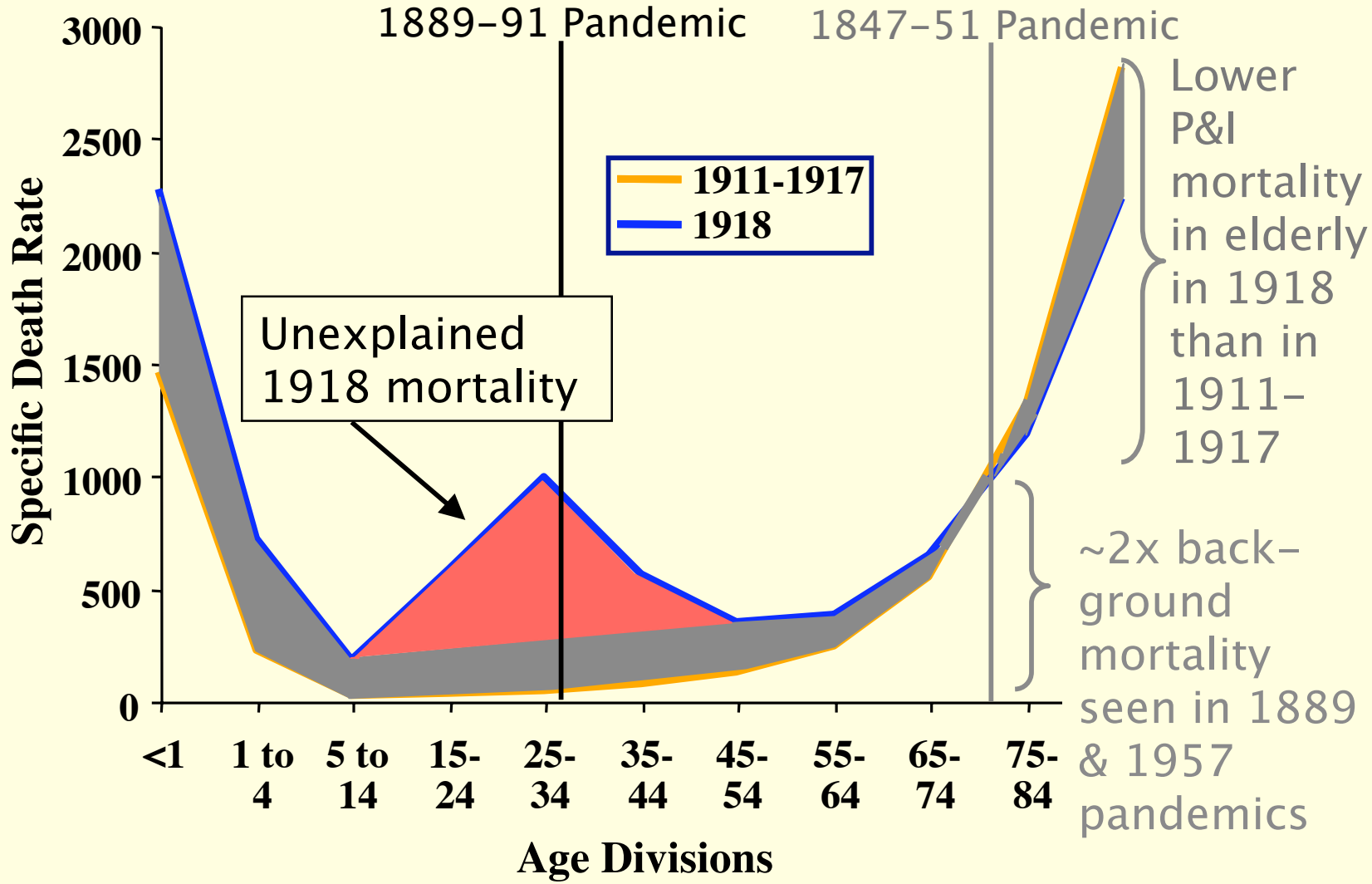
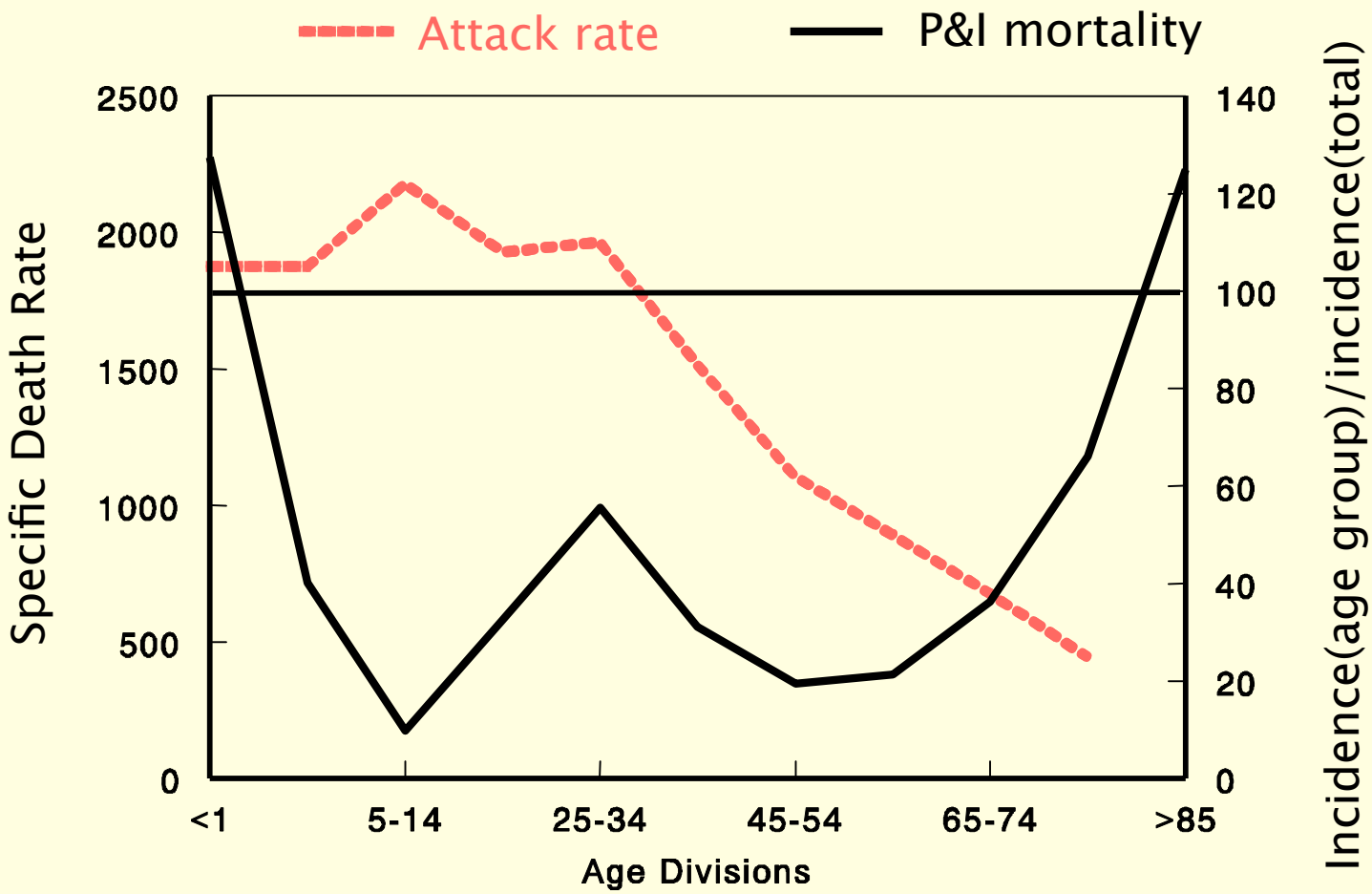


1918 Flu Incidence and Mortality by Age



Unique pattern of influenza and pneumonia deaths by age in 1918

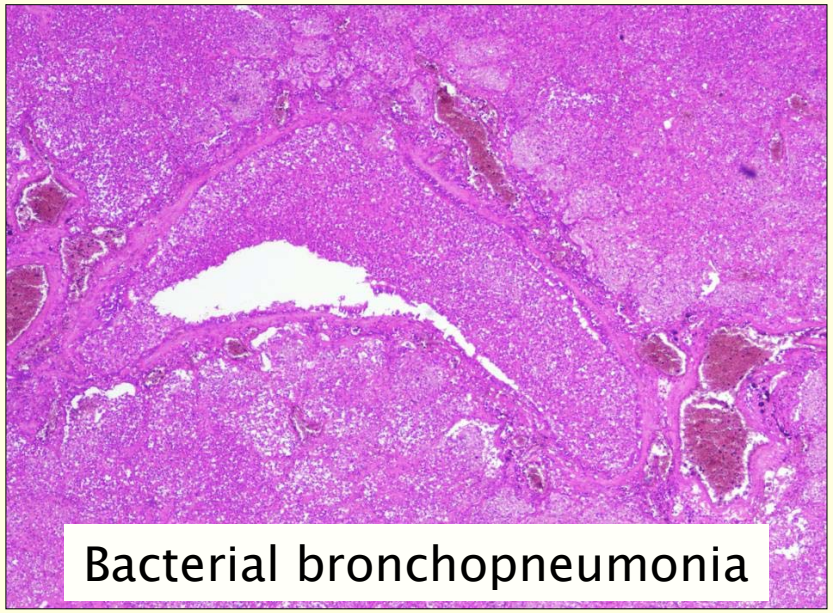
- W-shaped age specific mortality not explainable by intrinsic features of the virus
- Sharp increase in mortality in 18-35 year olds, with much lower mortality in 5-17 year olds (naïve to H1N1 and highest attack rate)
- Age-specific host factors most likely component to mortality not just inherent viral virulence:
  - e.g. Bacterial carriage rates (?)
  - e.g. Environmental factor (?)
  - e.g. Antibody-dependent enhancement (?)

Cause of death in 1918 influenza: Role of secondary bacterial pneumonias

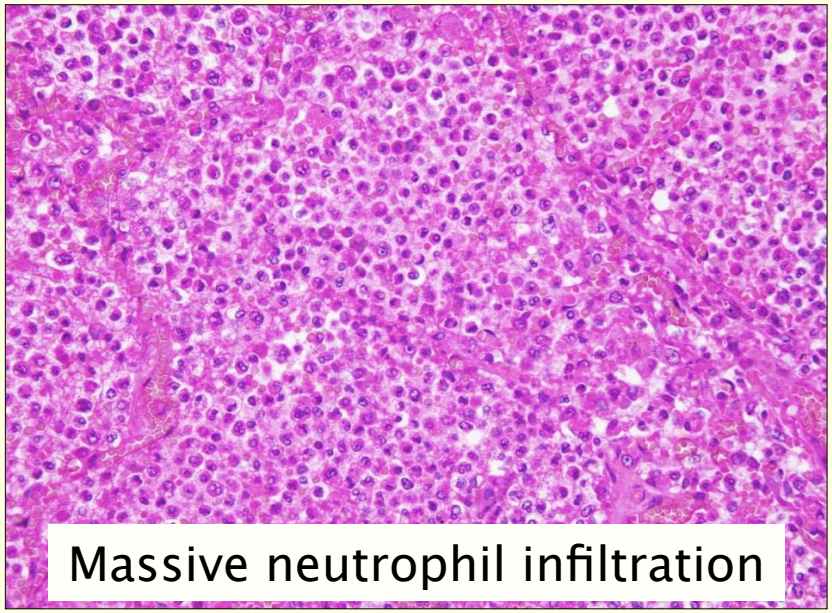
- Survey of 8,305 autopsies with postmortem cultures in 1918–1919 pandemic
- 97% postmortem lung cultures positive for one or more bacteria:
  - *Streptococci*, *Pneumococci*, or *Staphylococci* most common
- Average time course to death was ~14 days
- Majority of deaths in 1957 and 1968 pandemics also related to secondary bacterial pneumonia
- Range of pathologic changes in 1918 autopsies equivalent to 1957 and 1968 pandemic autopsies

Morens, Taubenberger & Fauci 2008 JID 98:962-70

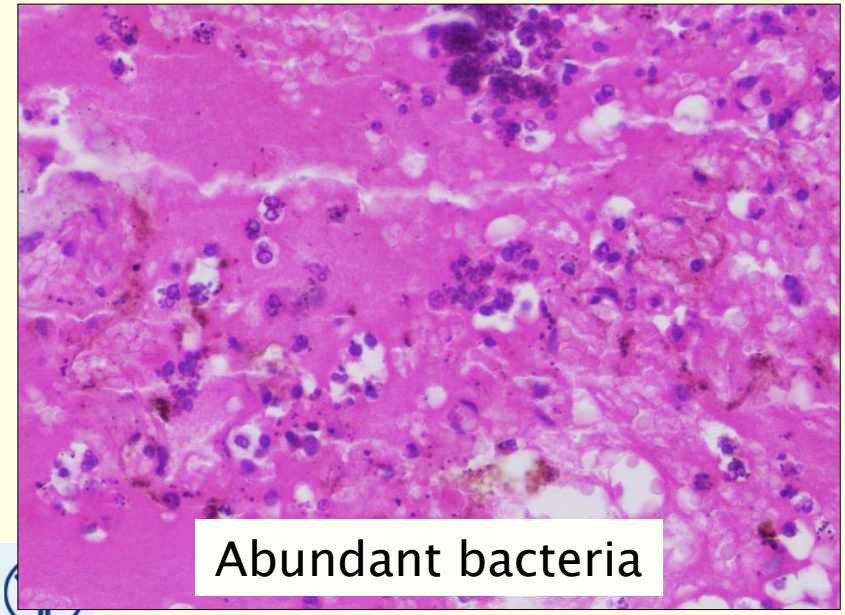
1918 autopsy findings



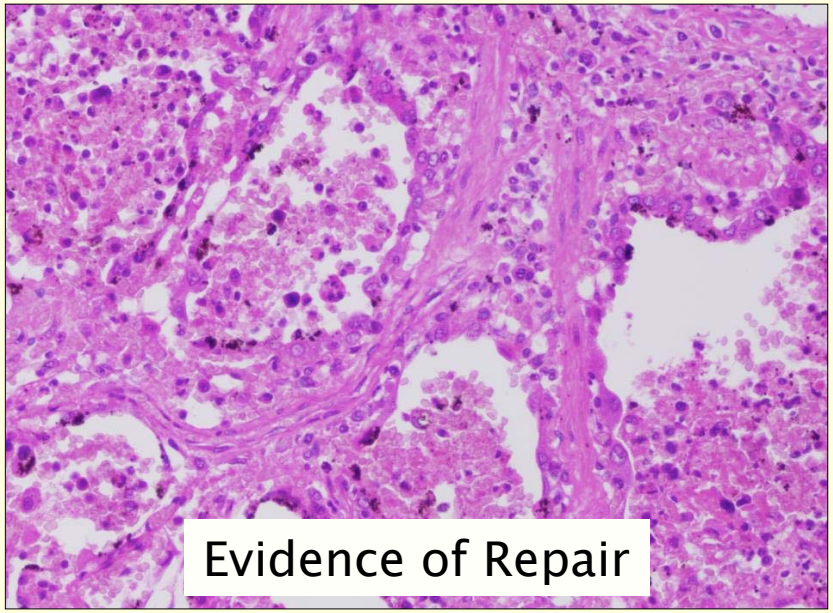
Bacterial bronchopneumonia



Massive neutrophil infiltration



Abundant bacteria



Evidence of Repair

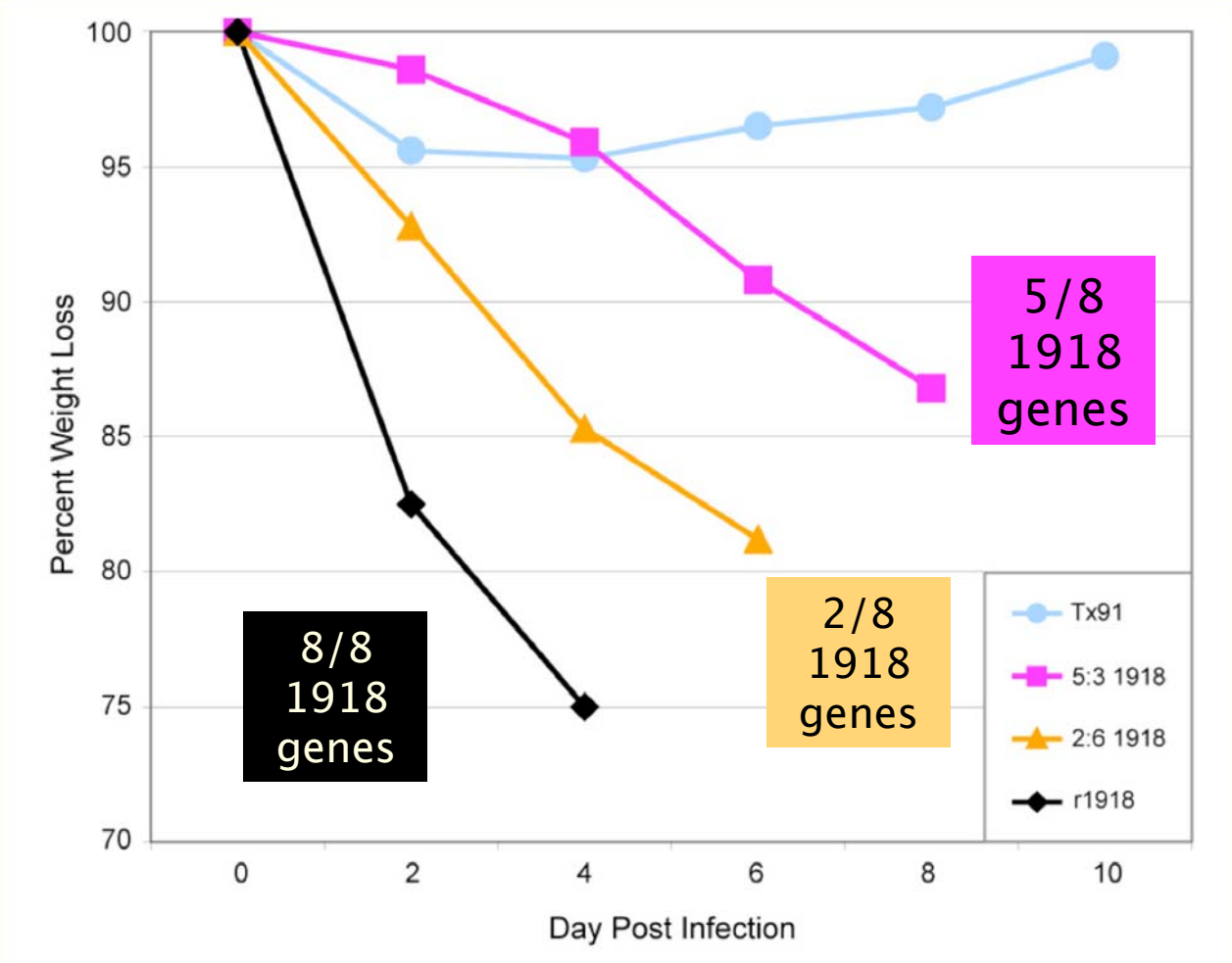
Relating Experimental Animal Models of Disease to Human Disease

- Case fatality rate in 1918 was ~2.5%
- High dose infections of 1918 virus in anesthetized mice lethal
- Most mouse strains interferon deficient (Mx−); infections in Mx^+ mice not lethal
- 1918 virus infections cause disease in ferrets and mice very similar to BSL2 A/swine/Iowa/1930 (closest related descendant virus)

Influenza viral pathogenicity is multi-factorial

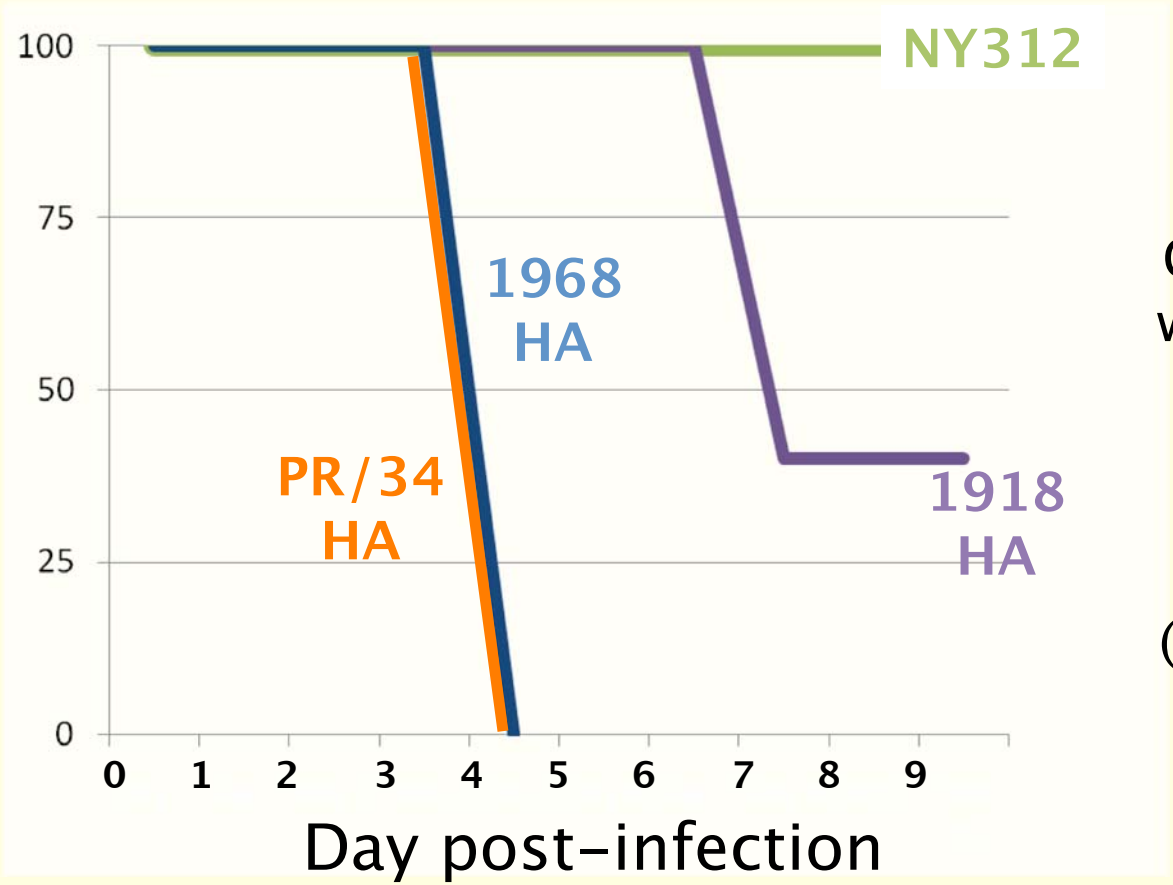
- Dependent on:
  - *Viral gene constellation*
  - *Animal host and genetics*
  - *Dose and route of administration*
- 1918 virulence is not unique in experimental animal models

Influenza virulence is polygenic and is dependent on the constellation of genes



Kash *et al* 2006 Nature 443:578

1918 HA is not a unique virulence factor

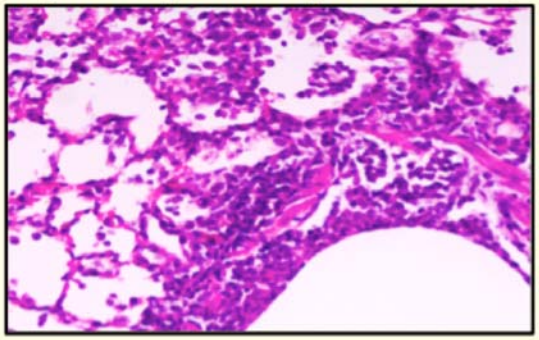
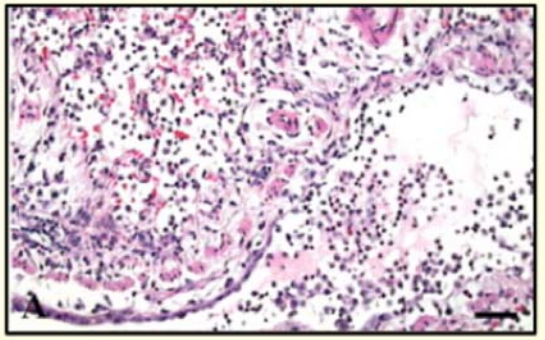
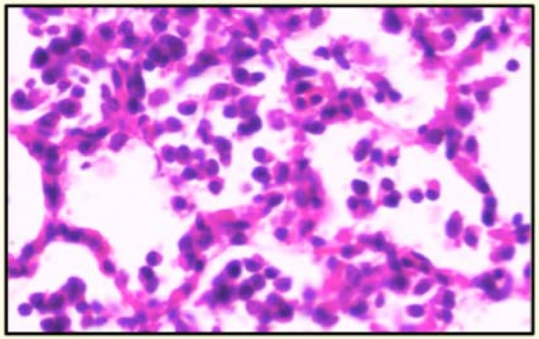
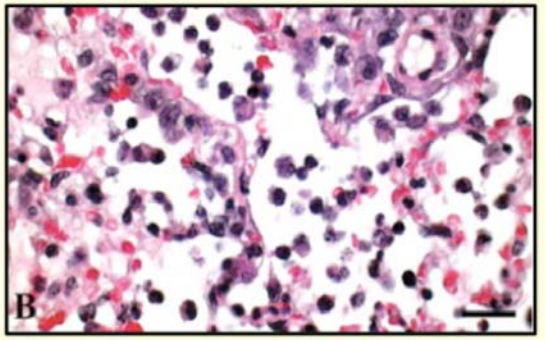
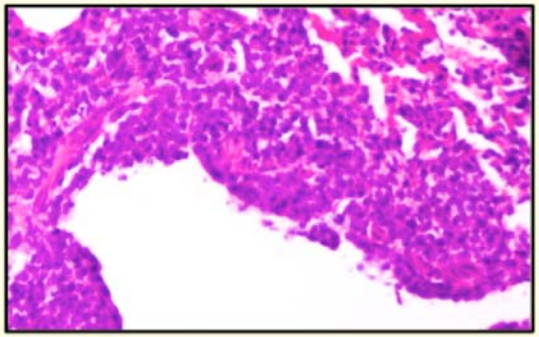
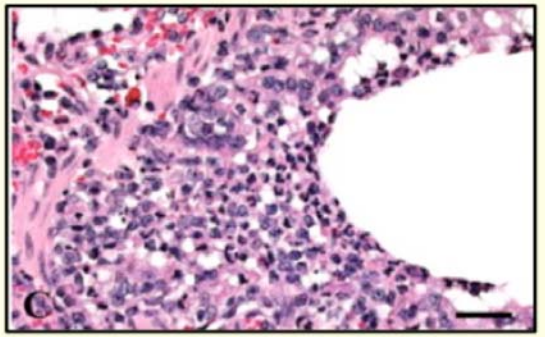


Chimeric viruses with different HA genes on backbone of a contemporary H1N1 (A/NY312/2001)

2 x 10^5 PFU *i.n.*

(Li *et al* 2008 Unpublished)

1918 virulence is not unique in ferrets

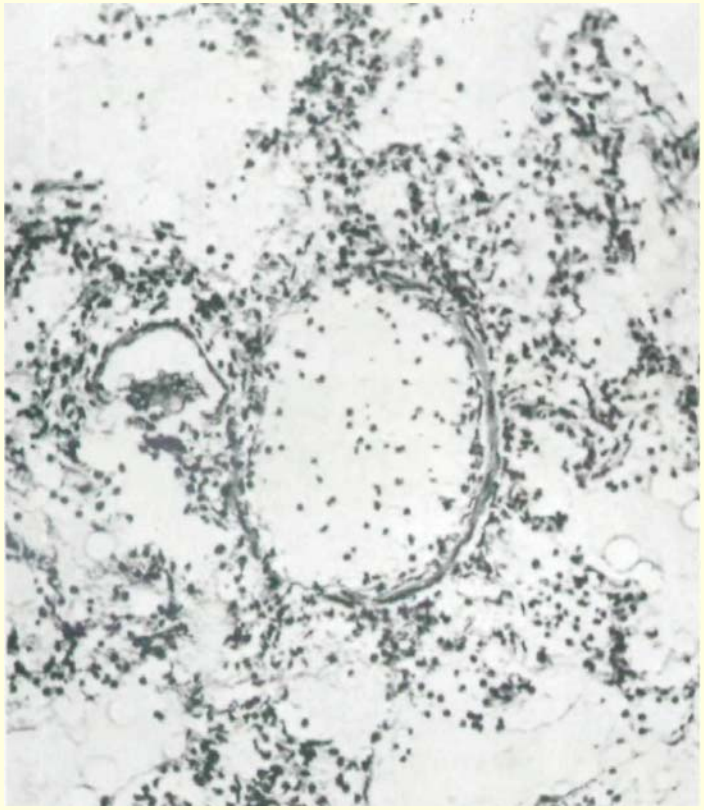
1×10^6 PFU A/Iowa/Swine/31 (BSL2)		1×10^6 PFU r1918 (BSL3+)
	Severe necrotizing bronchiolitis with severe diffuse alveolitis and edema	
	Severe diffuse alveolitis	
	Necrotizing bronchiolitis	

Memoli *et al* 2008 unpublished

Tumpey *et al* 2007 Science 315:655-9

1918 virulence is not unique in macaques

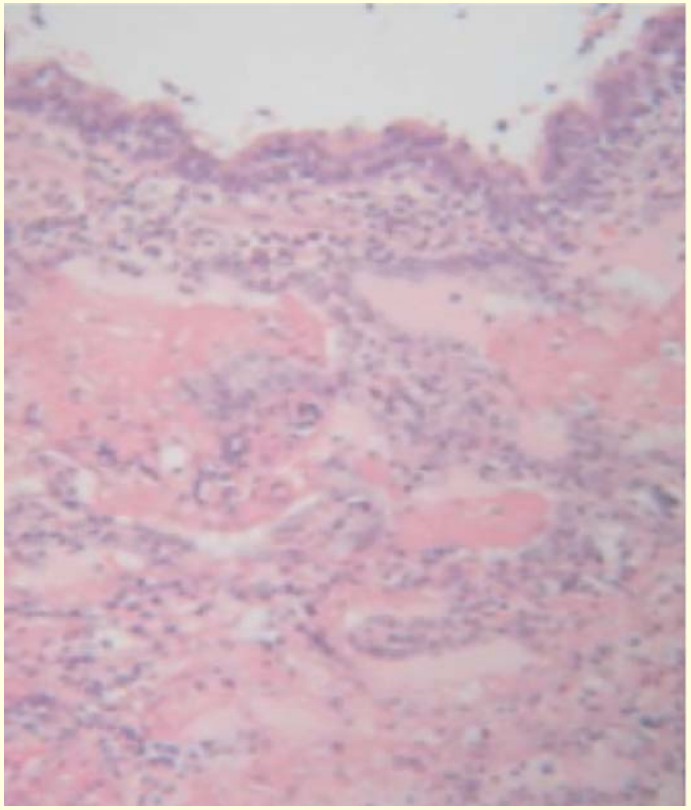
Lethal infection with A/Melbourne/40



FM Burnet 1941 *Aus J Exp Biol Med* 19:281-90

Necrotizing bronchiolitis and alveolitis

Lethal infection with r1918



Kobasa *et al*. 2007 Nature 445:319-323

Summary

- 1918 H1N1 viruses circulated until 1957, returning in 1977, and co-circulating with H3N2 since
- Vast majority of 1918 influenza cases with full recovery (97.5%)
- Vast majority of deaths following 1918 influenza infection caused by secondary bacterial pneumonias (97%)
- Long-lived immunoprotection:
  - Re-emergence of H1N1 in 1977 – only those <20 years old initially susceptible
  - Antibodies to 1918 virus in those born before 1918 (Yu *et al*. 2008 *Nature* 455:532-6.)
  - Likely immunoprotection in >65 population in 1918 due to circulation of H1 or N1 influenza viruses in the mid 19th Century